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RESEARCH PAPER

Effect of allopurinol on phosphocreatine recovery and muscle function in older people with impaired physical function: a randomised controlled trial

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Abstract

Background: Allopurinol has vascular antioxidant effects and participates in purinergic signalling within muscle. We tested whether allopurinol could improve skeletal muscle energetics and physical function in older people with impaired physical performance.
Methods: We conducted a randomised, double blind, parallel group, placebo-controlled trial, comparing 20 weeks of allopurinol 600 mg once daily versus placebo. We recruited community-dwelling participants aged 65 and over with baseline 6-min walk distance of <400 m and no contraindications to magnetic resonance imaging scanning. Outcomes were measured at baseline and 20 weeks. The primary outcome was post-exercise phosphocreatine (PCr) recovery rate measured using ^{31}P magnetic resonance spectroscopy of the calf. Secondary outcomes included 6-min walk distance, short physical performance battery (SPPB), lean body mass measured by bioimpedance, endothelial function and quality of life.
Results: In total, 124 participants were randomised, mean age 80 (SD 6) years. A total of 59 (48%) were female, baseline 6-min walk distance was 293 m (SD 80 m) and baseline SPPB was 8.5 (SD 2.0). Allopurinol did not significantly improve PCr recovery rate (treatment effect 0.10 units [95% CI, −0.07 to 0.27], $P = 0.25$). No significant changes were seen in endothelial function, quality of life, lean body mass or SPPB. Allopurinol improved 6-min walk distance (treatment effect 25 m [95% 4–46, $P = 0.02$]). This was more pronounced in those with high baseline oxidative stress and urate.
Conclusion: Allopurinol improved 6-min walk distance but not PCr recovery rate in older people with impaired physical function. Antioxidant strategies to improve muscle function for older people may need to be targeted at subgroups with high baseline oxidative stress.

Keywords: *allopurinol, physical performance, oxidative stress, skeletal muscle, older people*

Key Points

- Oxidative stress has been implicated in muscle dysfunction and allopurinol has been shown to reduce oxidative stress in other organ systems with clinical benefit.
- Allopurinol did not improve PCr recovery rate (a measure of skeletal muscle mitochondrial function).

- Six-min walk distance improved by a small but clinically significant amount but other measures of physical performance were unchanged.
- Future studies should target older people with high baseline levels of oxidative stress.

Introduction

Impaired physical performance is common with increasing age, and reduction in skeletal muscle function (part of the syndrome of sarcopenia) is a key contributor to this decline. Improving impaired physical function and preventing decline in physical function are key goals in maintaining health and wellbeing for a wide range of older people. Although regular exercise has been shown to increase muscle strength and to slow functional decline [1], the majority of older people are sedentary and often unable or unwilling to contemplate adequate exercise participation [2]. Alternative strategies to improve physical function are required to minimise dependency and maximise independence.

Allopurinol is a purine analogue that has been used to prevent gout for decades. It is a powerful inhibitor of xanthine oxidoreductase in both its forms—as xanthine dehydrogenase and as xanthine oxidase (XO). Inhibition of this key enzyme in the degradation of purines to urate lowers both urate as well as reactive oxygen species (ROS), which is a by-product of XO catalytic action. There are three reasons why allopurinol might be beneficial in ageing muscle. Firstly, skeletal muscle is particularly susceptible to oxidative stress mainly due to the rapid flux of oxygen and the balance of energy supply/demand. Previous studies have shown that oxidative stress is implicated in reduced quadriceps endurance [3]. XO is a major generator of free radicals; up-regulation of XO and increased oxidative stress are found in ageing muscles and this mechanism has been implicated in sarcopenia [4]. Therefore, reducing muscle oxidative damage might be expected to result in reduced muscle dysfunction, increased muscle contractile efficiency and reduced functional impairment.

Secondly, animal studies have previously demonstrated that allopurinol decreased free adenosine diphosphate (ADP) levels needed to drive adenosine triphosphate (ATP) synthesis, and normalised muscle phosphocreatine (PCr)-to-ATP ratio (PCr/ATP) [5]. These findings would be compatible with a beneficial effect of allopurinol on mitochondrial function, perhaps due to the reduction in oxidative stress described above. Suppression of XO with allopurinol has indeed been shown to increase maximal isometric force in plantar flexion in animal models [6], and allopurinol use was associated with greater functional gains in older patients undergoing rehabilitation in an observational study [7].

Thirdly, we have previously shown that allopurinol improves vascular endothelial function in various intervention studies enrolling older people with established cardiometabolic disease [8–11]. An improvement in muscle perfusion could also potentially improve muscle function, particularly given the high prevalence of vascular dysfunction found in older people. Therefore, we conducted this present study in older people with functional impairment to determine whether treatment with allopurinol could improve physical function, and to study the mechanism by which it might achieve this. We hypothesised that allopurinol would improve the initial rate of skeletal muscle PCr recovery after exercise (a measure of mitochondrial function) compared to placebo.

Methods

Study design

We performed a randomised, double-blinded, parallel-group, placebo-controlled trial between February 2016 and August 2017. Ethics approval was obtained from East of Scotland Research Ethics committee (approval number 14/ES/1092), and regulatory approval was obtained from the Medicines and Healthcare products Regulatory Agency (Clinical Trials Authorisation 2014-004122-18). It was carried out in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants at the screening visit. The trial was funded by Dunhill Medical Trust (Grant Ref: R315/1113) and trial management support was provided by Tayside Clinical Trials Unit. The trial was registered at www.isrctn.com (ISRCTN03331094).

Population and recruitment

Participants were eligible if they were aged 65 or over, with a 6-min walk distance of <400 m based on the study conducted by Newman *et al* [12]. Exclusion criteria were conditions likely to provide alternative causes for poor exercise tolerance and muscle dysfunction: a documented history of peripheral arterial disease, severe heart failure (left ventricular ejection fraction < 35%), malignancy under active treatment, severe chronic obstructive pulmonary disease (COPD) or long-term use of steroids (prednisolone equivalent of 10 mg/day or more). Other exclusion criteria were for safety reasons: intolerance to allopurinol, any use of allopurinol within the last 30 days, current use of azathioprine, 6-mercaptopurine or theophyllines or an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2 or less. Participants unable to perform the short physical performance battery (SPPB) or 6-min walk tests (6MWTs) without human assistance were excluded, as were those with contraindications to magnetic resonance imaging scanning, cognitive impairment precluding giving written informed consent, those who had participated in another clinical drug trial within the preceding 30 days and those with active acute gout. Participants were recruited via hospital outpatient clinics, newspaper advertisements to the local community and from primary care practice database searches conducted by the NHS Research Scotland Primary Care Network (NRSPCN).

Intervention and comparator

Matching capsules containing either 300 mg of allopurinol or placebo that appeared identical (Tayside Pharmaceuticals, Dundee, UK) were dispensed in identical bottles that had no indication of treatment allocation. Participants took one capsule each day for the first 4 weeks. If renal function remained stable and no side effects were noted, participants then took two capsules once a day for the remaining 16 weeks. Participants were permitted to continue their usual medication throughout the trial.

Randomisation and allocation concealment

Randomisation was performed in a 1:1 ratio by a web-based GCP compliant randomisation system (TRuST, Health Informatics Centre, University of Dundee) to ensure allocation concealment. A minimisation algorithm with a small random element was used to ensure balance across key baseline measures. Minimisation factors used were male versus female sex and baseline 6-min walk distance of less than or more than 200 m.

Outcomes

All outcomes were measured at baseline and at 20 weeks. Details of the methods used for outcomes measures are given in Supplementary Material A1 [13–20]. The pre-specified primary outcome was the initial rate of PCr recovery (ViPCR). Secondary outcomes were the 6-min walk distance [16], SPPB [17], lean body mass derived from bioimpedance using the Sergi equation [18], endothelial function [19] and health-related quality of life measured using the EQ5D tool [20]. All outcomes were assessed by a research fellow blinded to intervention group, and investigators remained blinded to treatment allocation until after completion of the statistical analysis.

Sample size calculation

The sample size was calculated based on detecting a 20% difference between groups in the primary outcome of initial PCr resynthesis rate (ViPCR). Data published by Layec *et al*. [3] showed ViPCr values in healthy older people (74 ± 17%/min) versus COPD patients (52 ± 13%/min) i.e. a 42% difference between healthy older people and patients with COPD. A conservative approach would be to assume that functionally impaired older people have less severe impairment than people with COPD. We therefore assumed 20% difference between healthy older people and functionally impaired older people on allopurinol. To detect this difference with 90% power at a significance level of $\alpha = 0.05$ requires 44 participants per group. Allowing for a 20% dropout rate, we required 110 participants. To ensure a further buffer against technical failure or uninterpretable MR spectroscopy results, the final sample size was set at 124 participants, which also gave sufficient power for key secondary endpoints to detect a 2% absolute difference in Flow-Mediated Dilatation (FMD) of the brachial artery [21] and the minimum clinically important difference of 20 m for the 6-min walk [22].

Analysis

All analyses were performed using SPSS v24 (IBM, New York, USA) according to a pre-specified statistical analysis plan. A P value < 0.05 was taken as significant for all analyses. Descriptive statistics were generated for both groups at baseline; comparisons between baseline groups were performed using Student's t-test for continuous variables if normally distributed, and Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square test. The primary and secondary analyses were performed by modified intention to treat, including all participants with follow-up data. For normally distributed variables, general linear models were used to compare results between groups at 20 weeks, adjusted for baseline values. Several of the magnetic resonance spectroscopy (MRS) variables were not normally distributed, but instead conformed to a gamma distribution. These variables were compared using generalised linear models, adjusting for baseline values of the variable under test, using a gamma distribution and log link function. Estimated marginal means were generated to convey treatment effect size. Several sensitivity analyses were performed for the primary outcome. Multiple imputations (10 imputations) were performed using baseline ViPCr, age, sex, baseline 6-min walk distance and SPPB to impute missing ViPCr values. A per-protocol analysis was also performed, including only those participants still taking the full dose of study medication at the final visit, and with adherence > 80%. Statistical analyses were performed blinded to treatment allocation, and unblinding of the analysis took place only after analysis completion.

Results

A total of 265 individuals expressed interest in participating, of whom 142 attended a screening visit and 124 were randomised. Baseline data on the randomised population are given in Table 1, and Figure 1 shows participant flow through the trial. A total of 116 individuals (58/62 in the allopurinol arm and 58/62 in the placebo arm) attended the final study visit. Adherence to the study medications was excellent; mean adherence in the allopurinol group was 93% (SD 12%), compared to 95% (SD 12%) in the placebo group ($P = 0.32$).

Primary outcome

There was no significant difference between the allopurinol and placebo groups in the ViPCR corrected for baseline ViPCr (Table 2).

Table 1. Baseline details

		Allopurinol ($n=62$)	Placebo ($n=62$)	P
Mean age (years) (SD)		79.9 (5.3)	80.6 (6.6)	0.55
Female sex (%)		29 (47)	30 (48)	0.86
Ischaemic heart disease (%)		8 (13)	12 (19)	0.33
Hypertension (%)		42 (68)	33 (53)	0.10
Dyslipidaemia (%)		34 (55)	33 (53)	0.86
Stroke or TIA (%)		7 (11)	6 (10)	0.77
Diabetes mellitus (%)		10 (16)	10 (16)	1.00
Median weekly alcohol intake (units) (IQR)		2 (1–8)	2 (0–5)	0.38
Current smoker (%)		3 (5)	5 (8)	0.47
Systolic BP (mmHg) (SD)		141 (15)	146 (20)	0.14
Diastolic BP (mmHg) (SD)		78 (10)	76 (10)	0.49
Body Mass Index (kg/m^2) (SD)		28.5 (4.6)	28.1 (4.9)	0.59
Six-min walk distance (m)		295 (80)	290 (79)	0.75
Muscle mass (kg) (SD)	Males	11.6 (2.3)	11.2 (2.4)	0.50
	Females	9.9 (1.8)	10.1 (1.6)	0.72
SPPB (SD)		8.6 (2.0)	8.4 (2.0)	0.69
Median total number of medications (IQR)		5 (3–8)	5 (3–8)	0.90
Medications:				
Angiotensin converting enzyme inhibitor		15 (24)	17 (27)	0.68
Beta blocker		9 (15)	12 (19)	0.47
Calcium channel blocker		22 (35)	17 (27)	0.33
Alpha blocker		7 (11)	5 (8)	0.76
Thiazide		14 (23)	15 (24)	0.83
Loop diuretic		5 (8)	5 (8)	1.00
Aldosterone antagonist		2 (3)	2 (3)	1.00
Angiotensin receptor blocker		6 (10)	5 (8)	0.75
Statin		29 (47)	23 (37)	0.28
Antiplatelet		14 (23)	16 (26)	0.68
Insulin		2 (3)	0 (0)	0.50
Antidiabetic		6 (10)	6 (10)	1.00

Independent t-test, Mann–Whitney test or Pearson's chi-squared (Fisher's exact where cell value is <5). SD, standard deviation; TIA, transient ischemic attack; IQR, interquartile range.

Table 2. Primary outcome: effect of treatment on measures of PCr recovery rate

		Allopurinol (median, IQR)	Placebo (median, IQR)	Treatment effect[a] (95% CI)	p
Normalised ViPCr	Baseline	0.50 (0.33–0.83)	0.60 (0.35–0.78)	0.10 (−0.07 to 0.27)	0.25
	20 weeks	0.60 (0.33–0.94)	0.59 (0.43–0.82)		
Sensitivity analyses					
Normalised ViPCr—multiply imputed				0.08 (−0.09 to 0.26)	0.36
Normalised ViPCr—per protocol	Baseline	0.50 (0.31–0.99)	0.54 (0.32–0.76)	0.10 (−0.07 to 0.27)	0.27
	20 weeks	0.63 (0.36–0.96)	0.58 (0.43–0.82)		
Un-normalised ViPCr	Baseline	23,385 (5419–38,668)	20,681 (3821–33,521)	5715 (−3674 to 15,104)	0.23
	20 weeks	28,227 (16818–51,171)	29,005 (17810–42,279)		

[a]Estimated marginal mean from generalised linear model using gamma distribution with log link. Multiple imputations (10 imputations) using baseline ViPCr, age, sex, baseline 6-min walk and SPPB to impute missing ViPCr.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses for the primary outcome are shown in Supplementary Material A2. The only significant subgroup interaction was with baseline 6-min walk distance, where those with the lowest walk distance ($<$200 m) showed deterioration in ViPCr with treatment, in contrast to those with a baseline walk distance of $>$300 m ($P=0.05$ for interaction). For the per-protocol sensitivity analysis, a total of 98 participants were included (44 in the allopurinol arm and 54 in the placebo arm). Results for this analysis are shown in Table 2.

Secondary outcomes

Non-MRS secondary outcomes are shown in Table 3. Allopurinol caused a large reduction in serum urate compared to the placebo group as expected. Six-min walk distance improved in the allopurinol group compared to placebo;

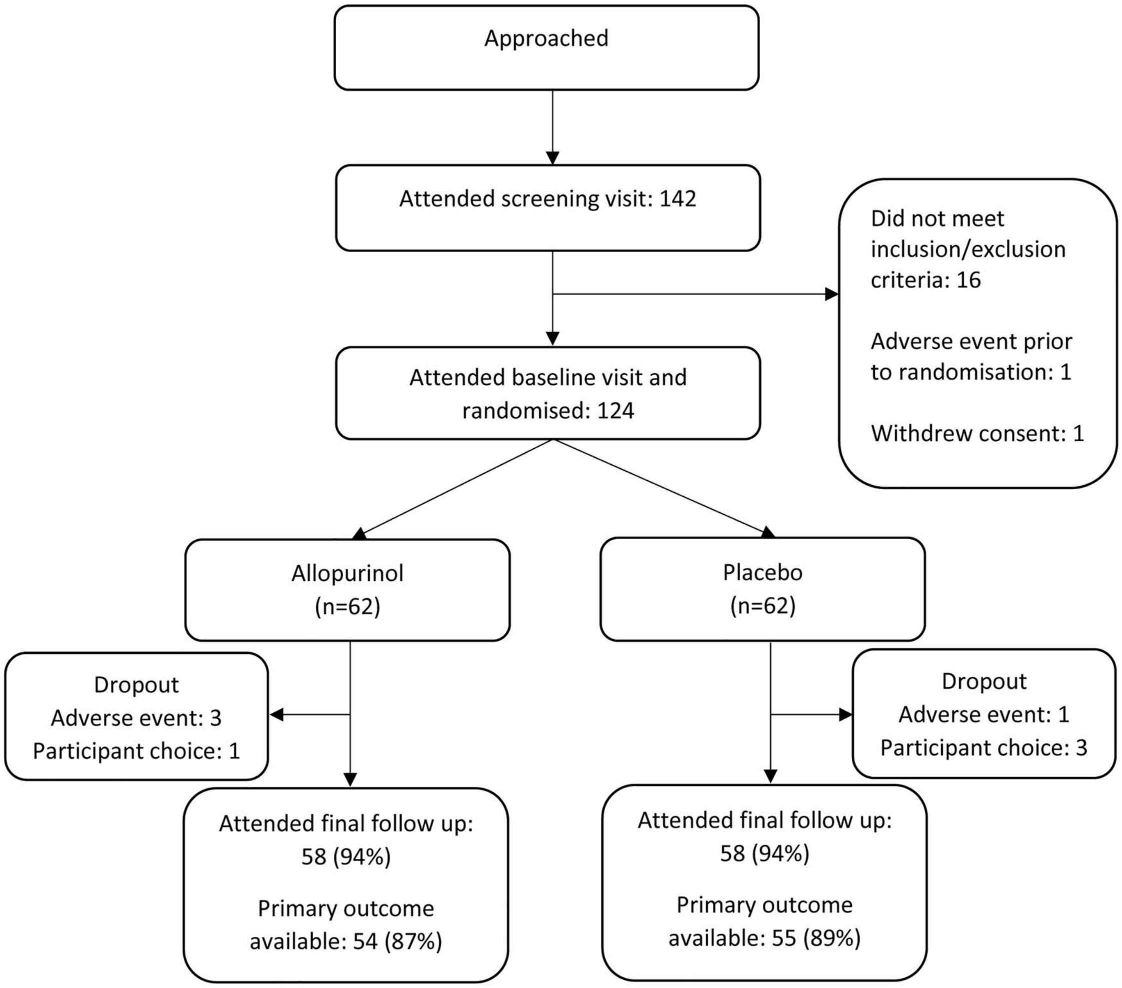

Figure 1. CONSORT diagram of participant flow through the trial

the treatment effect (25 m) was statistically significant and exceeded the minimum clinically important difference of 20 m. Post hoc exploratory subgroup analyses of the 6-min walk distance suggested that the difference in 6MWT was significantly greater in participants who had higher baseline muscle oxidative stress (8-hydroxydeoxyguanosine (8-OHDG) > 233 ng/ml) and baseline urate (>0.41 mmol/L) (Supplementary Material A3). A weak correlation (rho = 0.18, $P = 0.06$) was seen between change in ViPCr and change in 6-min walk distance. Other measures of oxidative stress, endothelial function, physical performance, lean body mass and quality of life did not improve with allopurinol relative to placebo. Alternative MRS measures of muscle energetics are shown in Supplementary Material A4; no significant treatment effect was seen on any marker.

Adverse events

Adverse events are shown aggregated into MedDRA system-organ-class categories in Supplementary Material A5. More adverse events were seen in the allopurinol arm, driven by a higher frequency of skin, gastrointestinal and vascular events.

Discussion

The main finding from this present study is that allopurinol did not improve muscle efficiency as measured by initial rate of PCr recovery in older participants with functional impairment. However, it improved the 6MWT distance and this improvement was more pronounced in those with a higher baseline oxidative stress and urate level. This would suggest that the mechanism of improvement may not be by ADP-sparing and improved PCr recycling but rather via an alternative antioxidant mechanism. We have previously demonstrated in a heart failure cohort that allopurinol at this high dose functions as an effective antioxidant, capable of abolishing Vitamin C-sensitive component of vascular oxidative stress [8]. Urate is an abundant and potent aqueous antioxidant in humans, although its importance as a major antioxidant *in vivo* is unclear [23,24]. It is possible that reducing urate in normouricemic patients with low background oxidative stress, who rely on urate for antioxidant defence, will negate any direct reduction in ROS generation by XO inhibition, leading to an overall null effect on oxidative stress, mitochondrial function and therefore PCr recovery. This could also explain the non-significant increase

Table 3. Secondary outcomes

		Allopurinol (SD)	Placebo (SD)	Treatment effect (95% CI)	*P*
Six-min walk (m)	Baseline	295 (80)	290 (79)	25 (4 to 46)	0.02
	20 weeks	366 (95)	340 (85)		
Lean body mass (kg/m^2)	Baseline	10.8 (2.3)	10.7 (2.1)	0.1 (−0.5 to 0.7)	0.70
	20 weeks	10.6 (2.0)	10.4 (2.0)		
SPPB	Baseline	8.6 (2.0)	8.4 (2.0)	0.0 (−0.5 to 0.5)	0.91
	20 weeks	9.3 (1.8)	9.1 (1.9)		
EQ5D health state	Baseline	0.78 (0.20)	0.77 (0.23)	0.02 (−0.03 to 0.07)	0.41
	20 weeks	0.81 (0.14)	0.80 (0.20)		
EQ5D thermometer	Baseline	78 (15)	78 (14)	2 (−2 to 6)	0.32
	20 weeks	79 (14)	78 (13)		
Systolic BP (mmHg)	Baseline	141 (15)	146 (20)	0 (−5 to 5)	0.94
	20 weeks	143 (15)	145 (17)		
Diastolic BP (mmHg)	Baseline	78 (10)	76 (10)	-1 (−4 to 2)	0.66
	20 weeks	76 (10)	76 (11)		
FMD[a] (%)	Baseline	7.50 (3.86)	7.59 (3.95)	−0.63 (−2.11 to 0.84)	0.39
	20 weeks	6.92 (3.07)	7.45 (3.69)		
FMD GTN (%)	Baseline	14.88 (5.55)	17.09 (5.50)	2.23 (−0.57 to 5.03)	0.12
	20 weeks	16.37 (5.30)	15.25 (6.64)		
Urate (mmol/L)	Baseline	0.38 (0.14)	0.42 (0.14)	−0.12 (−0.16 to 0.08)	<0.001
	20 weeks	0.24 (0.16)	0.40 (0.15)		
TBARS (uM)	Baseline	2.94 (1.51)	3.09 (1.34)	0.09 (−0.38 to 0.56)	0.70
	20 weeks	3.10 (1.68)	3.18 (1.51)		
8OHDG	Baseline	254 (107)	251 (104)	23 (−4 to 50)	0.10
	20 weeks	292 (140)	258 (104)		

BP, blood pressure; CI, confidence interval; EQ5D, EuroQoL 5-dimension score; FMD: flow-mediated dilatation of the brachial artery; GTN, glyceryl trinitrate; TBARS, thiobarbiturate reactive substances. [a]$n = 43$ for each group at baseline. Treatment effects adjusted for baseline value of variable under test.

in 8OHDG we saw with treatment. This phenomenon has been previously demonstrated in another normouricemic cohort with low oxidative stress [25].

We found an increase in the secondary outcome of 6MWT distance of 25 m in the allopurinol group compared to placebo. Perera *et al* [22] suggest that a 20 m gain in 6MWT is the minimum meaningful change in older people. In this present study, this difference in 6MWT was significantly greater in participants who had higher baseline muscle oxidative stress and baseline urate, which suggests that XO inhibition in these patients may be beneficial. The lack of effect of allopurinol on PCr recovery rate makes it unlikely that the improvement in 6-min walk distance was driven by improved mitochondrial function in normouricemic patients with low background oxidative stress. One alternative explanation is that allopurinol may have exerted improvements in exercise capacity via adenosine receptors present in a variety of tissues including the heart and skeletal muscle; it is noteworthy that caffeine (a molecule in the xanthine family) is known to have beneficial effects on exercise capacity. It is also possible that the improvement in 6-min walk distance was a chance finding due to testing multiple secondary outcomes; this finding requires replication in future trials.

Future studies in older people should focus interventions in those with high baseline oxidative stress and hyperuricemia. Unlike previous studies in cohorts with established disease [8,26], we did not observe an improvement in vascular endothelial function in this cohort which suggests that any functional improvement seen in this study is not directly attributable to improvements in muscle blood flow. Markers of ATP depletion such as the rate constant k, Pi/PCr ratio and amount of β-ATP depletion post-exercise were not significantly different between groups indicating that ATP sparing may not be the mechanism by which allopurinol improved walk distance.

Limitations

Preclinical work suggests that allopurinol might improve muscle function by reduction of XO-derived oxidative stress [6,27,28]. There are several reasons why we may not have detected this improvement in this present study. Only two men and no women met the clinical definition for sarcopenia and therefore it is possible that individuals with more impaired muscle physiology (i.e. those with sarcopenia) may have demonstrated greater improvement in muscle efficiency with allopurinol. The half-time recovery for PCr at baseline in our study was relatively preserved, suggesting that a ceiling effect may have limited the ability of allopurinol to improve measures of mitochondrial function. A previous study showed that patients with sarcopenia have impaired endothelial function, a measure upon which allopurinol has repeatedly demonstrated a beneficial effect [29]. We deliberately used a high dose of allopurinol to be sure that XO-derived oxidative stress was completely abolished; previous dose-response work in patients with heart failure suggests that 600 mg per day is required to achieve this [8]. The duration of therapy in our study was 20 weeks. It is possible but unlikely that a longer duration of action is required to demonstrate improvement in muscle efficiency if muscle oxidative stress reduction by XO inhibition is the mechanism by which it occurs. The positive effect on urate levels and improvement in 6-min walk distance argue in favour of this duration being long enough to produce relevant biological effects. Shorter durations of allopurinol therapy have shown improvements in endothelial function in previous studies [8,11], and as little as 1 week of allopurinol treatment improved skeletal muscle and mitochondrial function in preclinical models [6,30]. Muscle biopsies may have yielded more information on muscle oxidative stress but this option was declined by almost all patients and was therefore not pursued. Data acquisition for MRS commenced immediately post-exercise, potentially missing the very start of the recovery curve. Although we conducted the 6-min walk test only once at baseline and once at follow-up, the parallel-group design of our trial accounted for any learning effect, and thus the improvement in the allopurinol arm cannot be attributed to this.

In this present study, treatment allopurinol over 20 weeks did not improve muscle energetics as measured by MR spectroscopy. We observed a clinically relevant but modest increase in the 6MWT. Future studies could prospectively target those with sarcopenia, high urate and baseline muscle oxidative stress. Such an approach would be most likely to maximise the efficacy of allopurinol and would stand the best chance of both confirming any effect on walk distance and of elucidating the mechanism of any such effect.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: Allan D. Struthers has applied for a patent on the use of XO inhibitors to treat angina pectoris.

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